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PROPRIETARY DRUG NAME/INN: Bextra[®]/Valdecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

PROTOCOL NO.: A3471039

PROTOCOL TITLE: A Multicentre, Double-Blind, Double-Dummy, Randomised Study of the Analgesic Efficacy and Safety of Valdecoxib Compared to Diclofenac Sodium in Patients Undergoing Knee Arthroscopy Procedure for Anterior Cruciate Ligament Reconstruction

Study Center(s): Thirty two (32) centers in 9 countries enrolled patients in this study, including 2* in Australia, 2 in Hong Kong, 5 in Korea, 3 in Malaysia, 3 in New Zealand, 5 in the Philippines, 3 in Singapore, 4 in Taiwan, and 5 in Thailand.

*One study in Australia did not enroll patients.

Study Initiation and Completion Dates: 23 March 2004 - 01 September 2004

Phase of Development: Phase 4

Study Objective(s):

Primary:

- To demonstrate non-inferiority of valdecoxib 20 mg twice daily (BID) (with an initial loading dose of 40 mg followed by a second dose of 20 mg on the first day only) with diclofenac sodium delayed release 75 mg BID in analgesic efficacy, in subjects undergoing knee arthroscopy procedure for anterior cruciate ligament (ACL) reconstruction, when administered for 6 (\pm 1) days.

Secondary:

- To determine the safety of valdecoxib 20 mg BID (with an initial loading dose of 40 mg followed by a second dose of 20 mg on the first day only) compared to diclofenac sodium delayed release 75 mg BID, administered for 6 (\pm 1) days
- To evaluate the health outcome endpoints for subjects receiving valdecoxib or diclofenac sodium

METHODS

Study Design:

This was a multicenter, double-blind, double-dummy, randomised, parallel group study investigating subjects who had undergone uncomplicated arthroscopic ACL reconstruction and

CLINICAL STUDY SYNOPSIS

were experiencing post-operative pain meeting inclusion criteria. All subjects were required to attend the study center at screening (within 14 days prior to dosing) and on Days 1 (day of surgery) through 6 (± 1). Subjects were randomised to receive valdecoxib 20 mg BID (with an initial loading dose of 40 mg followed by a second dose of 20 mg on the first day only), or diclofenac sodium delayed release 75 mg BID for 6 (± 1) days. On the first day (day of surgery), the second dose of the study medication was omitted if the first dose was given after 6 pm. At least 4 hours must have elapsed between the 2 doses of study medication.

Number of Patients (planned and analyzed):

- *Planned:* A total of 312 subjects consisting of 156 per group were planned for this study.
- *Analyzed:* A total of 328 subjects were randomized; 163 subjects in the valdecoxib group and 165 in the diclofenac group were analyzed in the MITT and safety populations.

Diagnosis and Main Criteria for Inclusion:

Subjects had to be more than 18 years of age and have undergone an uncomplicated ACL reconstruction procedure and be in satisfactory health to be included in the study. In addition, they needed to have a baseline pain intensity of ≥ 50 mm on the VAS and “moderate to severe” pain on the categorical scale within 8 hours of the completion of the surgical procedure to be included.

Study Treatment:

Mean duration of treatment was 6 days in both groups.

- Valdecoxib tablets 20 mg twice daily (BID)
 - Initial loading dose of 40 mg followed by a second dose of 20 mg on the first day only
- Diclofenac sodium delayed release tablets 75 mg BID
- For both groups— 1 to 2 tablets tramadol 50 mg (rescue medication) as required every 6 to 8 hours; total not allowed to exceed 8 doses of 50 mg per day (24 hour period)

Efficacy Evaluations:

- *Primary Endpoint*
 - Patient Assessment of Pain- Visual Analog Scale (VAS)
The VAS consisted of a 100 mm line on which the patients could rate their pain from “worst pain” to “no pain”.
- *Secondary Endpoints*
 - Global Evaluation of Study Medication
 - Consumption of Rescue Medication

CLINICAL STUDY SYNOPSIS

Health Outcomes Evaluations:

- Modified Brief Pain Inventory – short form
- Effect on Pain Medication Questionnaire and Health Resource Utilization

Safety Evaluations:

Safety was measured by the record of adverse events, changes from Baseline in vital signs, and physical examination.

Statistical Methods:

Three populations were used to analyse the data.

Populations:

- Modified Intent to Treat (MITT): Subjects who were randomised into the study and who took at least 1 dose of study treatment.
- Per Protocol (PP): Subjects who satisfied all the MITT criteria, who had no major protocol deviation, and had both a baseline and a Day 6/final visit pain VAS score.
- Safety: Subjects who were randomised and received at least 1 dose of study treatment.

The safety population was used for all safety analyses.

Endpoints:

- Primary

The pain VAS score was summarised by treatment group over time (baseline to Day 6 and averaged over Day 1 [post first dose] to Day 6), and for Day 6/final visit (last observation carried forward [LOCF]), using means, medians, SDs, minimum values, and maximum values. The pain VAS data was also summarised graphically over time by treatment group using plots of means with 95% CIs. Confidence intervals were calculated for least square (LS) mean treatment difference on the Day 6/final visit (LOCF) measurements of the pain VAS using an analysis of variance (ANOVA) with treatment group and site fitted as factors. The PP population was the primary population for testing the hypothesis of non-inferiority on the pain VAS. The non-inferiority of valdecoxib to diclofenac sodium on the pain VAS was demonstrated if the upper limit of the 2-sided 95% CIs of the difference (valdecoxib – diclofenac sodium) was smaller than the pre-specified limit of non-inferiority of 10 mm. The analysis was repeated for the MITT population. These analyses were repeated using analysis of covariance (ANCOVA) with site and treatment fitted as factors, and the baseline value as a covariate.

CLINICAL STUDY SYNOPSIS

- Secondary

The MITT population was used for all secondary analyses.

- *Global Evaluation of Study Medication*

The number and proportion of subjects who fell into each response category of the Global Evaluation of Study Medication questionnaire was summarised by treatment group over time. Confidence intervals were calculated for LS mean treatment difference on the Day 6/final visit data using the same approach as that described for the Modified Brief Pain Inventory.

- *Consumption of Rescue Medication*

The consumption of rescue medication data was summarised by treatment group over time (Day 1 to 6 and cumulative total over the study period) using means, medians, SDs, minimum values, and maximum values. Confidence intervals were calculated for LS mean treatment difference on cumulative total consumption of rescue medication at Day 6 using the same approach as that described for the Modified Brief Pain Inventory.

- Health Outcomes Endpoints

- *Modified Brief Pain Inventory*

The number and percentage of subjects who reported having pain was tabulated by treatment group and study day. The number and percentage of subjects who ever reported having pain during Days 2 to 6 was also tabulated by treatment group. The 6 scores from the Modified Brief Pain Inventory were summarized. Confidence intervals were calculated for LS mean treatment difference on Modified Brief Pain Inventory scores at Day 6/final visit (LOCF) using ANOVA with treatment group and site fitted as factors. The assumptions of normality of residuals and homogeneity of variance were assessed with normal probability plots, and plots of residuals versus fitted values. Rectifying transformations or non-parametric methods were applied, if necessary.

- *Effects of Pain Medication Questionnaire*

A summary table was generated for the effects of pain medication questionnaire data showing the number and percentage of subjects who fell into each response category for each symptom (and worst category for any symptom) over time by treatment group. A summary table was generated showing the number and percentage of subjects who ever reported any symptoms according to maximum intensity during the course of the study by treatment group. Confidence intervals were calculated for LS mean treatment difference on cumulative total effects of pain medication score at Day 6 using the same approach as that described for the Modified Brief Pain Inventory.

- *Health Care Resource Utilisation*

The number of occasions where health professionals were contacted for any symptom was summed within subjects over the course of the study by contact type (*i.e.*, duty nurse/doctor called for, phone call/email, office visit, emergency department visits). These data were presented using means, medians, SDs, minimum values, and maximum values. The number and proportion of subjects

CLINICAL STUDY SYNOPSIS

who reported contact with a health professional at any time over the course of the study was calculated by symptom type (and overall) and tabulated. Multiple contacts over the course of the study for a particular symptom was counted only once in this analysis. Confidence intervals were calculated for LS mean treatment difference on cumulative total health care resource usage using the same approach as that described for the Modified Brief Pain Inventory.

RESULTS

Subject Disposition and Demography:

A total of 328 patients were randomized with 163 subjects being randomized to the valdecoxib group and 165 randomized to the diclofenac group. A total of 289 patients completed the study; this consisted of 152 in the valdecoxib group and 137 in the diclofenac group. The MITT population consisted of 163 patients in the valdecoxib group with 165 patients in the diclofenac group. The PP population was comprised of 143 patients in the valdecoxib group and 140 patients in the diclofenac group. Numbers of patients who withdrew from the study are detailed in Table S1.

Table S1 Reasons for Withdrawal

	Valdecoxib n=163 n (%)	Diclofenac n=165 n (%)
Discontinuations (total)	11 (6.7)	28 (17.0)
Related to Study Drug		
Adverse event	1 (0.6)	3 (1.8)
Lack of efficacy	0	2 (1.2)
Not Related to Study Drug		
Adverse event	0	2 (1.2)
Other*	6 (3.7)	8 (4.8)
Subject defaulted	4 (2.5)	13 (7.9)

*Included protocol violations, did not meet entrance criteria and incorrect drug administration

There were no significant differences between the treatment groups on demographics, vital signs or surgical procedures. A summary of the study population's gender, age and duration of surgery is provided in Table S2.

Table S2 Demography and Baseline Characteristics

	Valdecoxib n=163	Diclofenac n=165
Male (%)	139 (85)	147 (89)
Age, years (range)	29 (18-65)	28 (17-54)
Surgery, hours (range)	1.81 (0.5-4.25)	1.77 (0.5-4.50)

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CLINICAL STUDY SYNOPSIS

Efficacy Results:

Valdecoxib was shown to be non-inferior to diclofenac. The LS mean difference in pain VAS scores between treatment groups was -3.6 mm (95% CI: -8.0 to 0.8 mm) for the PP population.

Primary Endpoint:

The pain VAS results for both the PP and MITT groups are shown in Table S3.

Table S3 Pain VAS – PP and MITT Analysis Populations

	Valdecoxib		Diclofenac	
	Absolute mean (SD)	Change mean (SD)	Absolute mean (SD)	Change mean (SD)
PP Population	n=143		n=140	
Baseline	67.3 (13.00)		66.9 (12.26)	
Day 6	12.2 (15.33)	-54.7 (19.67)	13.8 (16.88)	-53.1 (20.15)
Day 6 (LOCF)	12.0 (16.02)	-55.5 (21.02)	15.9 (22.84)	-51.0 (24.70)
MITT Population	n=163		n=165	
Baseline	66.5 (13.51)		66.1 (13.00)	
Day 6	12.3 (15.78)	-53.9 (20.20)	13.2 (16.80)	-53.1 (20.25)
Day 6 (LOCF)	12.0 (16.19)	-54.5 (21.12)	15.5 (22.44)	-51.2 (24.60)

Secondary Endpoints:

Secondary endpoints are shown below in Table S4.

Table S4 Secondary Endpoints: Global Evaluation of Study Medication, Consumption of Rescue Medication – MITT Population

	Valdecoxib vs Diclofenac	
	Difference in LS means	95% CI
Global evaluation of study medication*	0.0	-0.1 to 0.2
Consumption of rescue medication, cumulative total*	-29.4 mg	-67.1 mg to 8.2 mg

*At Day 6/LOCF.

Health Outcomes Endpoints:

Health outcomes endpoints are shown below in Tables S5 and S6.

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CLINICAL STUDY SYNOPSIS

Table S5 Modified Brief Pain Inventory – MITT Population

	Mean score Day 2 (SD)		Mean score Day 6/LOCF (SD)		LS means (95% CIs)*
	Valdecoxib	Diclofenac	Valdecoxib	Diclofenac	
Incidence of pain (%)	153 (98.1)	139 (97.2)	121 (77.6)	113 (79.0)	—
Worst pain score	5.4 (2.35)	5.7 (2.60)	2.3 (2.14)	2.4 (2.27)	-0.1 (-0.5 to 0.4)
Least pain score	2.2 (1.81)	2.1 (1.75)	1.0 (1.33)	0.9 (1.19)	0.2 (-0.1 to 0.5)
Average pain score	3.6 (1.82)	3.6 (1.81)	1.6 (1.59)	1.6 (1.59)	0.0 (-0.3 to 0.4)
Current pain score	3.0 (2.00)	3.0 (2.10)	1.3 (1.57)	1.4 (1.74)	-0.0 (-0.4 to 0.3)
Relief of pain (%)	65.2 (21.75)	65.7 (23.53)	76.7 (24.74)	72.6 (29.62)	3.8 (-2.5 to 10.0)
Pain interference	3.3 (1.86)	3.2 (1.82)	1.3 (1.40)	1.1 (1.20)	0.2 (-0.1 to 0.5)

*Difference in LS means between treatment groups at Day 6/LOCF

Table S6 Effects of Pain Medication Questionnaire and Health Resource Utilization — MITT Population

	Valdecoxib vs Diclofenac	
	Difference in LS means	95% CI
Effects of pain medication questionnaire*	-1.9	-4.6 to 0.9
Frequency of contact with health care professionals	0.0	-0.3 to 0.3

*Total score aggregated over Days 2-6.

Safety Results:

The number of subjects with treatment emergent adverse events (AEs) was similar between treatment groups: valdecoxib n=75 (46.0%), diclofenac n=79 (47.9%) as was the number of treatment related AEs.

Table S7 summarizes the more common treatment emergent AEs ($\geq 5\%$ in either treatment group). Table S8 summarizes the discontinuations due to treatment related adverse events.

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CLINICAL STUDY SYNOPSIS

Table S7 Incidence of Adverse Events ($\geq 5\%$ in either treatment group) – Safety Population

Adverse Event n (%)	Valdecoxib n=163		Diclofenac n=165	
	All causality	Treatment related	All causality	Treatment related
Somnolence	27 (16.6)	12 (7.4)	30 (18.2)	13 (7.9)
Pruritus	21 (12.9)	10 (6.1)	14 (8.5)	6 (3.6)
Dizziness	15 (9.2)	5 (3.1)	19 (11.5)	10 (6.1)
Nausea	10 (6.2)	4 (2.5)	19 (11.5)	12 (7.3)
Constipation	11 (6.7)	3 (1.8)	17 (10.3)	8 (4.8)
Dysuria	10 (6.1)	1 (0.6)	15 (9.1)	4 (2.4)
Pyrexia	5 (3.1)	2 (1.2)	9 (5.5)	3 (1.8)

Table S8 Discontinuations Due to Treatment Related Adverse Events – Safety Population

Subject No.	Treatment	Adverse Event	Start/Stop Day	Outcome
10091008	Valdecoxib	Post procedural pain	1/2	Resolved
10031006	Diclofenac	Nausea	2/8	Resolved
		Vomiting	2/8	Resolved
		Drowsiness	2/8	Resolved
10091005	Diclofenac	Pain	1/2	Resolved
10251008	Diclofenac	Headache	1/>2	Still present

There were no SAEs or deaths in this study.

The median changes from baseline to last observation in systolic and diastolic blood pressure and heart rate showed small, observed changes with no clinically relevant differences arising between treatment groups.

CONCLUSION(S):

This was a multicenter, double-blind, double-dummy, randomized, parallel group study in subjects who had undergone uncomplicated arthroscopic ACL reconstruction, had post-operative pain greater than 50 mm VAS and “moderate to severe” pain on the categorical scale within 8 hours of the completion of surgery. Subjects received either valdecoxib 20 mg BID (with an initial loading dose of 40 mg followed by a second dose of 20 mg on the first day only) or diclofenac sodium delayed release 75 mg BID for 6 (± 1) days.

- The primary endpoint, patient assessment of pain VAS, demonstrated that the LS mean difference between valdecoxib and diclofenac was -3.6 mm, favoring valdecoxib, and the upper limit of the 95% CI (-8.0 to 0.8 mm) for the PP population

CLINICAL STUDY SYNOPSIS

was well within the pre-specified 10 mm non-inferiority margin, as was the analysis with the MITT population.

- Valdecoxib and diclofenac performed comparably on the secondary endpoints.
- Valdecoxib and diclofenac had similar safety profiles in relation to the number and type of AEs experienced by subjects in this study.
- Both treatments were safe and generally well tolerated.

Based on a report completed on: 28 February 2005